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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/534,376	03/24/2000	Kari Alitalo	28967/34140A	2155

7590 05/20/2003

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/534,376	ALITALO ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,11-37 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11-37 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14,17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-5, 7-9, 11-37 and 40 are pending in the instant application. Claim 13 has been amended as requested by Applicant in Paper Number 16, filed March 3, 2003.

Objection to Specification

2. The objection to the specification is withdrawn in view of Applicants' amendment.

Maintained Rejections

Double Patenting

3. Claims 1-5, 7-9, 11-37 and 40 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,361,946, for reasons of record in the previous Office Action, Paper No. 13, at pages 3-4. It is acknowledged that Applicants request the requirement for the Terminal Disclaimer be deferred until the scope and language of allowable claims has been settled, however until such time, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.1 Claims 5, 7-9 and 11-8 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of treatment of a patient in

need of modulation of Flt4 activity, for reasons of record in the previous Office Actions, Paper No. 9 at pages 8-9, and Paper No. 13 at pages 4-5, and below.

Applicants traverse the rejection and assert that the application teaches that VEGF-C as taught in the application is a ligand for the Flt4 (VEGFR-3 receptor), and that the teachings related to both Flt4 and VEGF-C provide guidance to identification of patients that will benefit from modulation of Flt4, that the specification teaches Flt4 is expressed on (and becomes largely restricted to) lymphateic vessels, and teaches that the patients in need of modulation of their lymphatics are candidates to receive the Flt4 ligand taught in the specification (pages 21 and 29 of the specification).

Applicants' arguments have been fully considered but are not deemed persuasive. Because there are a number of patients that may or may not benefit from modulation of Flt4 and/or their lymphatics but none are defined in the claims, there are no limitations which patients are included and which are excluded and no guidance provided to predictably determine which patients may benefit and which may not. It is suggested that the claims be amended by canceling the "identification of patient" phrases, so that they would read on adminstration just to a patient.

4.2 Claim 22 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record in the previous Office Action, Paper No. 13, at page 5.

On pages 4-5 of the response Applicants submit that they have filed a Budapest Treaty Declaration attached as Appendix D. The cover sheet for Appendix D was present in the response, however the declaration was missing. Therefore, the rejection is maintained.

Claims 19-27 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating endothelial cell growth comprising administering a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 and variants thereof, does not reasonably provide enablement for gene therapy, for reasons of record in the previous Office Action, Paper No. 13, at pages 5-6, and below.

Applicants traverse the rejection and assert that the prior art at the time that the application was filed (first claimed priority date in 1995) contained abundant teachings concerning gene therapy vectors, promoters, transcriptional elements and administration methods, and that a search of the Patent Office's own database identifies numerous issued patents, filed before August 1995, that are directed to adenoviral, adeno-associated viral, retroviral and other gene therapy vectors, and that presumptively under the law, were enabled as of their filing dates for whatever gene therapy materials and methods were claimed therein. Applicants also assert that a search of literature databases identifies numerous articles describing in vivo gene therapy studies, and that a patent application need not disclose what is well known in the art. Applicants also assert that contrary to the allegation that the specification lacks working examples, Example 29 of the application describes the in vivo expression of human VEGF-C protein in mice using the human K14 skin-specific promoter, in which intentionally over-expressed VEGF-C in the skin caused proliferation of lymphatic vessels in the skin and

also, a myelopoietic effect in the blood, and that this example demonstrates that the application provides sufficient guidance or evidence for using polynucleotides in vivo.

Applicants' arguments have been fully considered but are not deemed persuasive. Example 29 is not a working example of the invention, because this is not an example of gene therapy, but is a method of making transgenic mice that over-express the VEGF-C gene. Also, the state of the art of gene therapy at the time of the invention was low, with no unambiguous therapeutic benefits. Science News Report (Science 269, page 1050, column 2, paragraph 1, lines 6-15) states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models. Anderson (Scientific American, September 1995, pages 124-128) states that *in situ* therapy, is hampered by effective ways for implanting corrected genes into various organs, as the genes are not expressed sufficiently to produce sufficient quantities of protein. Blau et al. (The New England Journal of Medicine, Nov. 2, 1995, pages 1204, column 1-2 bridging sentences and page 1205, column 1-2, bridging paragraph and page 1207, second column) wrote that expression and delivery of the gene desired for treatment were seen as the hurdles yet to be overcome, and that thus far clinical trials have not shown convincingly that gene therapy is effective in treating disease in humans, and the field is still in its infancy.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner

LORRAINE SPECTOR
PRIMARY EXAMINER